

# Risk Factors for Pancreatic Adenocarcinoma and Prospects for Screening

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**Abstract:** Pancreatic cancer has one of the worst survival rates of any cancer and is the fourth leading cause of cancer mortality. Early detection and surgery are the patient's best chance for cure. However, symptoms are typically vague and occur when the cancer is unresectable. Population-based mass screening is not practical for this rare disease, though screening and early detection in asymptomatic high-risk patient populations may be indicated.

Pancreatic cancer has one of the worst prognoses of any type of cancer, with a 5-year survival rate of only 4.6% and a median survival rate of less than 6 months. Although pancreatic cancer accounts for less than 2% of new cancers, it is the fourth leading cause of cancer mortality and accounts for 6% of all cancer deaths.<sup>1</sup> The best chance for curing the disease is early detection and surgery, which has a 5-year survival rate of approximately 21% when combined with chemotherapy.<sup>2</sup> The frequent vagueness of symptoms and typically unresectable nature of the disease at the time of initial diagnosis are the Achilles heel of early detection. Population-based mass screening is not practical in a disease as rare as pancreatic cancer (which has an incidence of 8–12 per 100,000).<sup>1</sup> However, screening and early detection in asymptomatic high-risk groups may be indicated, and will be examined in further detail in this paper.

## Defining Early Pancreatic Cancer

Fewer than 20% of patients with pancreatic cancer present with potentially curable disease. The 5-year survival rate remains only

## Keywords

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approximately 20% in patients undergoing operation with curable intent.<sup>1,3</sup> The major determinants of survival are tumor size, lymph node status, and extrapancreatic perineural invasion.<sup>4-6</sup> Tumors less than 1 cm in size with no nodal involvement carry a significantly better prognosis; in fact, Japanese researchers have had excellent results with early-stage disease. Ariyama and associates reported a 100% 5-year survival rate in patients with tumors less than 1 cm in size.<sup>7</sup> In another study from Japan, at the time of resection, 26% of patients had T1 lesions (<2 cm), which conferred a 5-year survival rate of 48.1%, whereas T3 lesions (tumors extending beyond the pancreas but without involvement of the celiac axis or superior mesenteric artery) had only a 5-year survival rate of 27.9%.<sup>8</sup> Studies in the United States have reported a 5-year survival rate of approximately 21% for resected pancreatic cancers and a higher rate (28%) in the subgroup of tumors less than 3 cm in size.<sup>5</sup>

Pancreatic cancer must be detected at an early stage to have a chance of being cured, and therein lies the problem: patients typically become symptomatic when the disease is incurable, and furthermore, the diagnostic tools at our disposal are poor at detecting small lesions in the pancreas.

## Tools Currently Available for Early Detection of Pancreatic Cancer

### *Serologic Tumor Markers*

Carbohydrate antigen 19-9 (CA 19-9) exists in tissue as an epitope of sialylated Lewis<sup>a</sup> blood group antigen. Most clinicians are aware of the use of CA 19-9 as a marker of pancreatic cancer but are not necessarily aware of its sensitivity, specificity, and positive predictive value. Approximately 5% of individuals, those who are genotypically Lewis<sup>a-b</sup>, lack the enzyme necessary to synthesize CA 19-9, further limiting its sensitivity.<sup>9</sup> CA 19-9 lacks the sensitivity for detecting early pancreatic cancer and is elevated in only 50% of pancreatic adenocarcinomas less than 3 cm in size.<sup>10</sup> In addition, data indicate that poorly differentiated pancreatic cancers may produce lower levels of CA 19-9 compared to well-differentiated tumors.<sup>10</sup>

CA 19-9 is also not specific for pancreatic cancer. It may be elevated in gastric cancer, colorectal cancer, cholangiocarcinoma, and urothelial malignancy, as well as in benign conditions such as biliary obstruction, hepatitis, acute and chronic pancreatitis, and thyroiditis.<sup>11-15</sup>

Among symptomatic patients, CA 19-9 has a sensitivity of 81–85% and a specificity of 81–90% when a cutoff of 37 U/mL is used.<sup>10,16</sup> As a screening test, CA 19-9 would be more useful in the asymptomatic population, but, unfortunately, it has a low positive predictive value. In a South Korean asymptomatic population, Kim and

colleagues found its sensitivity and specificity to be excellent (100% and 98.5%, respectively) but noted a positive predictive value of only 0.9%, making CA 19-9 a very poor screening tool in asymptomatic patients.<sup>17</sup> The American Society of Clinical Oncology does not recommend the use of CA 19-9 as a screening test for pancreatic cancer.<sup>18</sup> Several other tumor markers, including K-ras, p53, and mucin, have been investigated; however, none of these markers is sensitive enough to be recommended for clinical use.

### *Pancreatic Imaging*

**Computed Tomography** Although computed tomography (CT) is important as a screening tool, almost all of its studies have been performed in symptomatic patients. The sensitivity of CT ranges from 20% to 89%,<sup>19,20</sup> depending upon the tumor size. From a screening perspective, CT is poor at detecting lesions less than 1–2 cm in size<sup>21</sup> and pancreatic adenocarcinoma in the background of chronic pancreatitis.

The quality and speed of CT imaging has significantly improved with the introduction of multidetector row spiral CT (MDCT). Furthermore, the use of a higher injection rate of iodinated contrast material (at 8 mL/sec) optimizes the bolus of intravenous dye to the faster acquisition speed of MDCT scanners. Compared to the standard flow rate of 4 mL/sec, this change results in greater pancreatic enhancement and greater conspicuity of the tumor relative to the background pancreas.<sup>22</sup> MDCT enables high-resolution three-dimensional imaging, and coronal multiplanar images have become a routine component of the CT staging of pancreatic neoplasm.<sup>23-25</sup> Curved coronal images are ideal for displaying the full length of the pancreatic duct that leads to an obstructing mass or for unfolding a tortuous vessel to show a perivascular tumor abutting the walls of the superior mesenteric vein, superior mesenteric artery, or celiac artery branches.<sup>26,27</sup> Coronal maximum-intensity projections are useful to show narrowing of the portal-splenic-mesenteric venous confluence and associated venous collaterals that engorge the branches of the gastocolic venous trunk.<sup>28-30</sup> Helical CT is superior to magnetic resonance imaging (MRI) for preoperative staging of pancreatic carcinoma. To determine surgical resectability, CT imaging shows invasion of peripancreatic tissue, portal and superior mesenteric veins, and peripancreatic arteries more reliably than MRI.<sup>31</sup>

The advantage of CT over MRI applies to patients with definite pancreatic carcinoma. CT imaging in a screening program of asymptomatic patients raises concerns regarding radiation dose, particularly the cumulative radiation dose of annual CT screening.<sup>32</sup> Therefore, MRI of the pancreas, without any ionizing radiation,

offers advantages for imaging the pancreas in a screening population.

**Magnetic Resonance Imaging** The role of MRI for evaluation of pancreatic malignancy continues to evolve. According to a meta-analysis of 68 studies, Bipat and coworkers found that for the detection of pancreatic adenocarcinoma, MRI had a sensitivity of 84% compared to 91% for helical CT, whereas the sensitivity for tumor resectability was essentially equal for both (MRI: 82%; CT: 81%).<sup>33</sup> However, the publication years for the cited articles ranged from 1990 to 2003. With the significant technological advancements with MRI and CT that have occurred since that time period, it is difficult to draw conclusions from this study. For MRI, these advances include the development of high-performance multi-channel phased-array coils and parallel imaging acquisitions, which allow for more rapid imaging sequences. In addition, the advent of the three-dimensional gradient-echo pulse sequence for dynamic postcontrast imaging as well as three-dimensional magnetic resonance cholangiopancreatography have allowed for increased spatial and contrast resolution, as well as decreased artifacts, with resultant improved visualization of the pancreas.<sup>34</sup> A more recent study by Park and associates concluded that MRI was superior to CT in the detection of pancreatic carcinoma and that both modalities performed similarly with respect to the evaluation of tumor resectability.<sup>35</sup> Moreover, with its superior contrast resolution, MRI has been shown to more reliably detect smaller, noncontour-deforming tumors compared to CT<sup>21,36</sup> and can more accurately detect and characterize smaller hepatic metastases.<sup>37,38</sup> With respect to screening, MRI is limited by its relatively higher cost, reduced availability, requirement for intravenous contrast administration, and increased examination time. However, the possibility of customized, unenhanced examinations at reduced cost and acquisition time are possible with advanced sequences such as diffusion-weighted imaging.<sup>39</sup> Therefore, supplementary studies, and perhaps additional innovation, are required for understanding the efficacy of MRI as a screening modality.

**Endoscopic Ultrasound** Endoscopic ultrasound (EUS) is the most sensitive test for detecting pancreatic cancer. This conclusion is supported by multiple studies,<sup>19,40,41</sup> including one by Müller and colleagues that noted a sensitivity of 94% for all cases and 93% for lesions less than 3 cm in size.<sup>19</sup> DeWitt and coworkers reported similar findings in a study comparing EUS to CT in 80 patients with pancreatic cancer. EUS had a sensitivity of 98% compared to 86% for CT.<sup>40</sup> However, EUS is usually performed after CT or MRI has already detected a

pancreatic mass; without this advantage, the reliability of EUS in a widespread screening program is less certain. EUS occasionally suffers from a limited field of view with relative blind spots in the uncinate process or tail of the pancreas.

**Endoscopic Retrograde Cholangiopancreatography** Endoscopic retrograde cholangiopancreatography (ERCP) is an excellent method for visualizing the pancreatic duct, with a sensitivity of 96% and specificity of 92% for diagnosing pancreatic cancer.<sup>16</sup> ERCP also has the potential for tissue sampling from the pancreatic duct. The shortcomings of ERCP as a screening tool include its invasive nature and significant morbidity.<sup>42</sup>

**Positron Emission Tomography** Fluorodeoxyglucose positron emission tomography (FDG-PET) relies on the increased uptake and metabolism of the radionuclide <sup>18</sup>F-fluorodeoxyglucose by neoplastic cells. FDG-PET has a sensitivity of 88–92% and a specificity of 83–85%<sup>43,44</sup> for pancreatic cancer, but it lacks anatomic detail. The combination of FDG-PET and CT adds the anatomic detail and localization that PET by itself lacks.<sup>45,46</sup> PET may miss lesions when they are desmoplastic or when there are not enough hypermetabolic tumor cells to accumulate glucose. The disturbance of glucose metabolism in diabetics also reduces the sensitivity of PET. The future role of PET in screening for pancreatic cancer is doubtful. PET will likely continue to have a limited role in pancreatic cancer staging, assessment of response to chemotherapy, and diagnosis of recurrent disease.

**Molecular Analysis of Pancreatic Juice** Pancreatic cancer biomarkers may be detected in pancreatic juice. Sampling of pancreatic juice is performed at the time of ERCP and carries the risk of inducing pancreatitis. In a study by Yan and associates, pancreatic juice was extracted in 146 patients with either pancreatic cancer, chronic pancreatitis, or biliary tract stones.<sup>47</sup> The pancreatic juice was analyzed for the p53 and k-ras mutations as well as the proportion of p16(INK4a) promoter methylation. Combination molecular analysis increased the discrimination between patients with malignant disease and those with benign disease and allowed patients in high-risk groups to be stratified from negligible risk to an over 50% probability of early cancer.<sup>47</sup> Nakashima and colleagues measured human telomerase reverse transcriptase (hTERT) expression in the pancreatic juice of 115 patients with pancreatic adenocarcinoma preoperatively.<sup>48</sup> hTERT expression was detected in 84% of pancreatic adenocarcinoma patients, whereas only 62% were positive based upon cytology. The European Registry of Hereditary Pancreatic and Familial Pancreatic Cancer

is currently studying the molecular analysis of pancreatic juice with CT and EUS as part of a secondary screening program. The limiting factor in the application of biomarkers from pancreatic juice is the invasive test required for sample collection.

### Considerations for a Screening Strategy

Screening for a disease in an asymptomatic patient involves many considerations. The disease for which patients are being screened should have a substantial morbidity and mortality. Pancreatic cancer certainly meets these criteria.<sup>1</sup> Early detection should improve prognosis. There is evidence that this statement is true in pancreatic cancer and that it is not merely due to lead-time bias.<sup>1,5-8</sup> Next, the pretest probability of a disease and the target population should be defined. The annual incidence of pancreatic cancer in the general population is only 0.01%.<sup>1</sup> According to Bayes' theorem, a disease with such a low prevalence dramatically reduces the post-test probability of having the disease, even when using a test with a high sensitivity and specificity. The cost, acceptability, and efficiency of a screening strategy should be considered. An affordable serologic test with a high sensitivity and specificity would be acceptable and efficient. A positive serologic test could lead to combinations of other tests, each with their own potential for harm that must be considered when a screening strategy is designed. Even if one considers the devastating prognosis of pancreatic cancer, it is difficult to conceive that mass population screening for such a rare disease would be feasible. Certain populations are at a much higher risk for pancreatic cancer, to the extent that screening may become feasible.

### Populations at Risk for Pancreatic Cancer

#### Inherited Risk Factors (Table 1)

**Hereditary Pancreatitis** Hereditary pancreatitis is an autosomal dominant condition that was first described by Comfort and Steinberg in 1952.<sup>49</sup> These patients usually present with recurrent attacks of acute pancreatitis starting in childhood and progress to chronic pancreatitis at a relatively young age. In 1996, Whitcomb and coworkers reported that mutations in the cationic trypsinogen gene (*PRSS1*) were associated with hereditary pancreatitis.<sup>50</sup> Mutations in this gene prevent inactivation of trypsin, resulting in autodigestion of the pancreas. More than 25 mutations in the *PRSS1* gene have been described to date. A less common mutation involves the pancreatic secretory trypsin inhibitor gene (*PSTI*), also known as the serine protease inhibitor Kazal type 1 (*SPINK1*). Mutations in this gene have been associated with chronic pancreatitis in children, tropical pancreatitis, and alcoholic chronic pancreatitis.

**Table 1.** Inherited Risk Factors for Pancreatic Cancer

	Risk for pancreatic cancer
Hereditary pancreatitis	52 <sup>51</sup>
Cystic fibrosis	31.5 <sup>57</sup>
Peutz-Jeghers syndrome	132 <sup>60</sup>
Hereditary nonpolyposis colorectal cancer with <i>MLH1</i> mutation	<6 <sup>64,65</sup>
Familial atypical multiple mole melanoma syndrome	13.1 <sup>68</sup>
Hereditary breast and ovarian cancer	23.1 in <i>BRCA1</i> carriers <sup>70,102</sup> 5.9–6.6 in <i>BRCA2</i> carriers <sup>70,71</sup>
Familial pancreatic cancer	6.4–32 <sup>54</sup>

Patients with hereditary pancreatitis have an estimated lifetime risk of 40% for developing pancreatic cancer.<sup>51</sup>

**Familial Pancreatic Cancer** In 1989, Lynch and coworkers described 12 families in which pancreatic cancer occurred in 2 or more first-degree relatives.<sup>52</sup> Subsequently, tumor registries were established to collect data on families with pancreatic cancer. Familial pancreatic cancer is defined as ductal adenocarcinoma of the pancreas affecting at least 2 first-degree relatives who do not fulfill the criteria for another inherited tumor syndrome.<sup>53</sup> The ongoing National Familial Pancreas Tumor Registry estimates the risk of developing pancreatic cancer in an individual with 2 affected family members to be 6.4-fold (95% confidence interval [CI], 1.8–16.4). With 3 or more affected family members, the risk may be as high as 32-fold (95% CI, 10.2–74.7).<sup>54</sup> Kindreds of families with sporadic pancreatic cancer appear to not have an increased risk of pancreatic cancer. There is evidence for anticipation of familial pancreatic cancer that does not appear to be the result of biases and is independent of smoking.<sup>55</sup> As of yet, there has been no identification of a gene that plays a major role in the development of familial pancreatic cancer, except for *BRCA2*, which is present in a minority of cases (17%) of familial pancreatic cancer.<sup>56</sup>

**Cystic Fibrosis** Cystic fibrosis is one of the most commonly inherited diseases of the exocrine pancreas. These patients are at a higher risk for digestive tract cancers (odds ratio [OR], 6.5; 95% CI, 3.5–11.1).<sup>57</sup> The frequency of pancreatic cancer in cystic fibrosis families is increased compared to that of the normal population; however, it is still very low.<sup>58</sup> Neglia and coworkers found

only 2 cases of pancreatic cancer in 28,000 individuals with cystic fibrosis.<sup>57</sup>

### Hereditary Syndromes Associated With Pancreatic Cancer

**Peutz-Jeghers Syndrome** Peutz-Jeghers syndrome is a rare autosomal dominant condition characterized by mucocutaneous pigmentation and hamartomatous gastrointestinal polyps. These patients are also at risk for developing gastrointestinal and extragastrointestinal cancers. The most common cause of Peutz-Jeghers syndrome is a germline mutation in the *STK11/LKB1* gene, which is involved in regulation of cell proliferation and polarity.<sup>59</sup> The increased risk of these patients for developing pancreatic cancer is as high as 132-fold (95% CI, 44–261), with a lifetime risk of 36%.<sup>60</sup>

**Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)** Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant condition associated with predominantly right-sided colorectal cancers at a relatively young age.<sup>61</sup> Patients are also at risk for noncolorectal cancer, including pancreatic,<sup>62</sup> ovarian, gastric, endometrial, and small-bowel cancer.<sup>63</sup> HNPCC is caused by a mutation in one of the DNA mismatch repair genes, the most common being *MLH1* and *MSH2*. The relative risk (RR) for developing pancreatic cancer in patients with HNPCC is less than 6.<sup>64,65</sup> In a study of Korean and Dutch patients with HNPCC, pancreatic cancer was only found in patients with the *MLH1* mutation.<sup>66</sup>

**Familial Atypical Multiple Mole Melanoma** Familial atypical multiple mole melanoma (FAMMM), also known as dysplastic nevus syndrome, is an autosomal syndrome presenting with numerous dysplastic nevi or melanomas. Approximately 50% of patients with this syndrome have germline mutations in the cyclin-dependent kinase 2A (*CDKN2A*) gene, which appears to be required for the development of pancreatic cancer.<sup>67</sup> These patients have a 13.1-fold (95% CI, 1.5–47.4) increased risk for pancreatic cancer.<sup>68</sup>

**Melanoma-Pancreatic Cancer Syndrome** A family was identified in 1995 who had pancreatic cancer and melanoma associated with the *CDKN2A* gene, but without the phenotype of FAMMM. This situation is now regarded as a cancer syndrome distinct from FAMMM.<sup>69</sup>

**Hereditary Breast and Ovarian Cancer** Carriers of the *BRCA1* or *BRCA2* germline mutations have an increased risk of pancreatic cancer, though the risk is greater for carriers of the *BRCA2* mutation. According to Risch and associates, the RR of pancreatic cancer is 3.1 (95%

CI, 0.45–21) and 6.6 (95% CI, 1.9–23) in carriers of the *BRCA1* and *BRCA2* mutations, respectively.<sup>70</sup> Van Asperen and colleagues calculated a RR of 5.9 (95% CI, 3.2–10) in carriers of the *BRCA2* mutation.<sup>71</sup>

### Noninherited Risk Factors (Table 2)

**Smoking** Tobacco smoking increases the risk of pancreatic cancer up to 2.5-fold compared to that of nonsmokers, and has been noted in up to one third of pancreatic cancer patients.<sup>72,73</sup> The risk appears to be dose-related but does drop off significantly after cessation of smoking.<sup>72,74</sup> It has been suggested that smoking cessation could prevent 25% of the deaths attributed to pancreatic cancer in the United States.<sup>72</sup>

**Diabetes Mellitus** Pancreatic cancer occurs with increased frequency among individuals with diabetes.<sup>75–77</sup> A meta-analysis of 36 studies found that type 2 diabetes increases the risk of pancreatic cancer by 82% (OR, 1.82; 95% CI, 1.66–1.89).<sup>77</sup> The risk of pancreatic cancer was 50% higher if diabetes was diagnosed within the preceding 5 years.<sup>77</sup> Although earlier studies have focused on type 2 diabetics,<sup>78</sup> a recent meta-analysis by Stevens and coworkers found that type 1 diabetes increased the risk of pancreatic cancer 2-fold (RR, 2.0; 95% CI, 1.37–3.01).<sup>76</sup> Chari and associates estimated that 1% of diabetic subjects over 50 years of age will be diagnosed with pancreatic cancer within 3 years of meeting diagnostic criteria for diabetes.<sup>79</sup> The high prevalence of diabetes in the general population excludes hyperglycemia as a practical screening tool for pancreatic cancer. Hyperglycemia may become more relevant as a screening test if it becomes possible to differentiate pancreatic cancer–induced diabetes from other causes of hyperglycemia by means of better clinical characteristics or the use of serologic markers.

**Chronic Pancreatitis** Chronic pancreatitis is a progressive inflammatory disease characterized by irreversible histologic transformation that clinically presents with pain or loss of function.<sup>80</sup> Most cases of chronic pancreatitis are secondary to excessive alcohol consumption,

**Table 2.** Noninherited Risk Factors for Pancreatic Cancer

	Risk for pancreatic cancer
Smoking	1.6–2.5 <sup>72–74</sup>
Diabetes	2.0 for type 1 diabetes <sup>76</sup> 1.8 for type 2 diabetes <sup>77</sup>
Chronic pancreatitis	18.5 <sup>81</sup> –26.3 <sup>83</sup>
Obesity	1.72 <sup>86</sup>

yet only 5–10% of chronic alcoholics develop chronic pancreatitis. Therefore, the causal relationship is not straightforward. Other dietary, environmental, and genetic factors likely play a role. Much less frequent causes include any obstructions of the pancreatic duct such as a traumatic disruption, pancreas divisum, stones, or tumors. Tropical pancreatitis and autoimmune pancreatitis are recognized causes of chronic pancreatitis, as are certain systemic conditions such as hypertriglyceridemia and hyperparathyroidism. Chronic pancreatitis may be part of a familial syndrome.

Chronic pancreatitis elevates the risk of pancreatic cancer, which increases over time.<sup>81–83</sup> Quantifying the risk is difficult because of confounding factors such as smoking, alcohol, and diet. The standard incidence ratio has been estimated to be between 18.5<sup>81</sup> and 26.3.<sup>83</sup> Stated in more meaningful terms, Lowenfels and coworkers found the cumulative risk to be 1.8% after 10 years and 4% after 20 years.<sup>83</sup> Tropical pancreatitis is an even greater risk for pancreatic cancer, with a RR of 100 (95% CI, 37–218).<sup>84</sup> In hereditary pancreatitis, the risk is also very high, with a cumulative lifetime risk of 40%.<sup>51</sup>

**Obesity and Physical Activity** Excessive body weight appears to increase the risk of pancreatic cancer.<sup>85–87</sup> The Health Professionals Follow-up Study and the Nurses Health Study found that men and women with a body mass index (BMI) of at least 30 kg/m<sup>2</sup> had a 72% increased risk of pancreatic cancer when compared to those with a BMI of less than 23 kg/m<sup>2</sup> (RR, 1.72; 95% CI, 1.19–2.48).<sup>86</sup> Physical activity appeared to reduce the risk of pancreatic cancer by 55% (RR, 0.45; 95% CI, 0.29–0.70). In Cancer Prevention Study II, the risk of pancreatic cancer was 41% higher in subjects with a BMI between 30.0 kg/m<sup>2</sup> and 34.9 kg/m<sup>2</sup> (RR, 1.41; 95% CI, 1.19–1.66) when compared to those with a normal BMI (<25 kg/m<sup>2</sup>).

**Cystic Lesions of the Pancreas** Cystic neoplasms of the pancreas are a frequent incidental finding due to the increased use of high-resolution cross-sectional abdominal imaging. The most common cystic neoplasms of the pancreas are serous or mucinous in nature. Serous cystic neoplasms of the pancreas have a characteristic honeycomb appearance on CT scan, MRI, and ultrasound, and they do not have malignant potential. In 1996, mucinous cystic neoplasms were classified by the World Health Organization as either mucinous cystic neoplasms (MCNs) or intraductal papillary mucinous neoplasms (IPMNs), both of which have the potential for malignant transformation.<sup>88</sup> MCNs are usually solitary neoplasms, occur almost exclusively in women, and are usually found in the pancreatic body or tail. MCNs contain ovarian

type stroma and, therefore, require surgical resection and histologic examination to make a definitive diagnosis.<sup>89</sup> IPMNs affect men and women equally, are usually located in the head of the pancreas, and may be multiple. IPMNs arise from the pancreatic duct and can be classified as main-duct IPMNs, side-branch IPMNs, or a mixed phenotype. Main-duct IPMNs are characterized by dilation of the main duct (>1 cm), whereas side-branch IPMNs consist of side-branch mucinous cysts without main duct involvement. A connecting side branch between the cyst and the main pancreatic duct is frequently identified on pancreatic imaging. Mixed IPMNs have features of both main-duct and side-branch IPMNs. The distinctions between the three types of IPMNs are important, as main duct involvement carries significant malignant potential and the need for resection, whereas branch-duct IPMNs of less than 3 cm and without mural nodules can be managed conservatively.<sup>89</sup> A more detailed discussion of the management of pancreatic cystic neoplasms is beyond the scope of this review and has been published elsewhere.<sup>90–92</sup>

### Evidence From Published Screening Studies in Asymptomatic High-risk Populations

Several models have evaluated the possible benefits of screening in high-risk populations. Rulyak and associates used a decision analysis protocol to compare a one-time EUS screening for pancreatic dysplasia with no screening in a hypothetical cohort of 100 familial pancreatic cancer patients.<sup>93</sup> They concluded that EUS was cost-effective and increased life expectancy, provided that the population was at high risk, with a prevalence of dysplasia over 16% and a sensitivity of EUS over 84%. On the other hand, a similar model devised by Rubenstein and colleagues looked at 4 management strategies: no surveillance, total pancreatectomy, EUS surveillance, and EUS with biopsy, based upon a 45-year-old man with a first-degree relative with pancreatic cancer and a history of chronic pancreatitis.<sup>94</sup> Although the lifetime risk of cancer was 20%, no surveillance provided the lowest cost and the greatest remaining quality and years of life. Total pancreatectomy was only beneficial if the lifetime risk of cancer was 46%. This study demonstrated the weakness of any screening approach in pancreatic cancer: even with early diagnosis, the mortality is high; thus, early diagnosis does not have an impact on life expectancy.<sup>95</sup>

Only a few series have looked at screening in asymptomatic high-risk populations. In 14 patients with a family history of pancreatic cancer in first-degree relatives, Brentnall and coworkers diagnosed 7 patients with pancreatic dysplasia based upon a combination of patient history, EUS, and ERCP, which was confirmed pathologi-

cally at the time of pancreatectomy.<sup>96</sup> At the University of Washington, 46 patients in familial pancreatic cancer kindreds have been screened by EUS.<sup>97</sup> Changes of chronic pancreatitis were found in approximately half of the patients. ERCP was performed on those with abnormal EUS findings. If a pancreatography was found to be abnormal, pancreatectomy was recommended. In all pathologic specimens, widespread dysplasia was found, but no invasive cancer.

Canto and coworkers studied 2 groups with a high risk of pancreatic cancer (patients with Peutz-Jeghers syndrome and relatives of patients in familial pancreatic cancer kindreds).<sup>98</sup> A total of 78 patients and 149 control subjects were evaluated with a baseline and 12-month EUS and CT scan. If the EUS was abnormal, EUS–fine-needle aspiration and ERCP were performed. Abnormalities suggestive of chronic pancreatitis were common in the high-risk groups (78% by EUS and 73% by ERCP). Seventeen high-risk patients were diagnosed with neoplastic-type lesions on EUS. Eight of these patients had pancreatic neoplasms diagnosed by fine-needle aspiration or surgery. In 7 patients who underwent surgery, branch-duct-type IPMNs were diagnosed pathologically. The authors commented that IPMNs should be considered part of the phenotype of familial pancreatic cancer. In this study, ERCP and CT were inferior to EUS for the detection of small precursor lesions.

A recent series of 44 asymptomatic patients with a combination of hereditary risk factors for pancreatic cancer were screened using EUS. Three (6.8%) patients were found to have mass lesions that were resected and identified as adenocarcinoma. Seven patients (16%) were diagnosed with premalignant lesions. In this series, EUS screening was feasible and safe; however, the impact on long-term survival was unclear.<sup>99</sup>

## Conclusions

Although there are no standard screening guidelines for patients at high risk of pancreatic cancer, astute physicians can potentially diagnose early cases if they are aware of the risk factors for pancreatic cancer and collaborate with a radiologist and endoscopist experienced in pancreatic diseases.

Familial pancreatic cancer and Peutz-Jeghers syndrome are perhaps closest to having established screening guidelines. It has been suggested that relatives from familial pancreatic cancer kindreds start screening at 40 years of age or 10 years before the youngest family member with pancreatic cancer.<sup>97,98</sup> Because patients with Peutz-Jeghers syndrome develop pancreatic cancer at an even earlier age, screening should begin at ages 25–30.<sup>100</sup> The optimal frequency of screening has not been criti-

cally assessed, though several institutions recommend annual screening.<sup>98</sup>

Of all the candidate tests for detecting early pancreatic cancer in high-risk individuals, EUS is the most sensitive. However, EUS is expensive, invasive, operator-dependent, and impractical for mass screening on a large scale. The ideal screening tool would be a molecular marker detected in the blood of patients with early stage, or surgically resectable disease, such as the plasma marker recently reported.<sup>101</sup> However, any such marker has yet to be validated. The improved sensitivity of radiologic imaging such as CT and MRI are exciting and, when combined with 1 or more blood markers, may allow for earlier detection.

Although mass screening for pancreatic cancer is not feasible at this point in time, it is important that we continue to strive for earlier diagnosis of pancreatic cancer. Clinicians should at least be aware of the noninherited and inherited risk factors for pancreatic cancer, as this knowledge may allow more targeted screening on an individual basis.

## References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, et al. Cancer statistics, 2006. *CA Cancer J Clin*. 2006;56:106-130.
2. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200-1210.
3. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet*. 2004;363:1049-1057.
4. Nakao A, Harada A, Nonami T, Kaneko T, Takagi H. Clinical significance of carcinoma invasion of the extrapancreatic nerve plexus in pancreatic cancer. *Pancreas*. 1996;12:357-361.
5. Yeo CJ, Cameron JL, Lillemoe KD, Sitzmann JV, Hruban RH, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg*. 1995;221:721-731; discussion 731-733.
6. Millikan KW, Deziel DJ, Silverstein JC, Kanjo TM, Christein JD, et al. Prognostic factors associated with resectable adenocarcinoma of the head of the pancreas. *Am Surg*. 1999;65:618-623; discussion 623-624.
7. Ariyama J, Suyama M, Satoh K, Sai J. Imaging of small pancreatic ductal adenocarcinoma. *Pancreas*. 1998;16:396-401.
8. Egawa S, Takeda K, Fukuyama S, Motoi F, Sunamura M, Matsuno S. Clinicopathological aspects of small pancreatic cancer. *Pancreas*. 2004;28:235-240.
9. Tempero MA, Uchida E, Takasaki H, Burnett DA, Stepelwski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res*. 1987;47:5501-5503.
10. Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. *Am J Gastroenterol*. 1990;85:350-355.
11. Parra JL, Kaplan S, Barkin JS. Elevated CA 19-9 caused by Hashimoto's thyroiditis: review of the benign causes of increased CA 19-9 level. *Dig Dis Sci*. 2005;50:694-695.
12. Chuang C-K, Liao S-K. Evaluation of CA19-9 as a tumor marker in urothelial malignancy. *Scand J Urol Nephrol*. 2004;38:359-365.
13. Mihmanli M, Dilege E, Demir U, Coskun H, Eroglu T, Uysalol MD. The use of tumor markers as predictors of prognosis in gastric cancer. *Hepatogastroenterology*. 2004;51:1544-1547.
14. Fuszek P, Lakatos P, Tabak A, Papp J, Nagy Z, et al. Relationship between serum calcium and CA 19-9 levels in colorectal cancer. *World J Gastroenterol*. 2004;10:1890-1892.
15. Pavai S, Yap SE. The clinical significance of elevated levels of serum CA 19-9. *Med J Malaysia*. 2003;58:667-672.

16. Niederau C, Grendell JH. Diagnosis of pancreatic carcinoma. Imaging techniques and tumor markers [see comment]. *Pancreas*. 1992;7:66-86.
17. Kim JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population [see comment]. *J Gastroenterol Hepatol*. 2004;19:182-186.
18. Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer [see comment]. *J Clin Oncol*. 2006;24:5313-5327.
19. Müller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. *Radiology*. 1994;190:745-751.
20. Hessel SJ, Siegelman SS, McNeil BJ, Sanders R, Adams DF, et al. A prospective evaluation of computed tomography and ultrasound of the pancreas. *Radiology*. 1982;143:129-133.
21. Saisho H, Yamaguchi T. Diagnostic imaging for pancreatic cancer: computed tomography, magnetic resonance imaging, and positron emission tomography. *Pancreas*. 2004;28:273-278.
22. Schueller G, Schima W, Schueller-Weidekamm C, Weber M, Stift A, et al. Multidetector CT of pancreas: effects of contrast material flow rate and individualized scan delay on enhancement of pancreas and tumor contrast. *Radiology*. 2006;241:441-448.
23. Brennan DD, Zamboni GA, Raptopoulos VD, Kruskal JB. Comprehensive preoperative assessment of pancreatic adenocarcinoma with 64-section volumetric CT. *Radiographics*. 2007;27:1653-1666.
24. Catalano C, Laghi A, Fraioli F, Pediconi F, Napoli A, et al. Pancreatic carcinoma: the role of high-resolution multislice spiral CT in the diagnosis and assessment of resectability. *Eur Radiol*. 2003;13:149-156.
25. Brügge M, Link TM, Rummeny EJ, Lange P, Theisen J, Dobritz M. Assessment of vascular invasion in pancreatic head cancer with multislice spiral CT: value of multiplanar reconstructions. *Eur Radiol*. 2004;14:1188-1195.
26. Fukushima H, Itoh S, Takada A, Mori Y, Suzuki K, et al. Diagnostic value of curved multiplanar reformatted images in multislice CT for the detection of resectable pancreatic ductal adenocarcinoma. *Eur Radiol*. 2006;16:1709-1718.
27. Vargas R, Nino-Murcia M, Trueblood W, Jeffrey RB Jr. MDCT in pancreatic adenocarcinoma: prediction of vascular invasion and resectability using a multiphasic technique with curved planar reformations. *AJR Am J Roentgenol*. 2004;182:419-425.
28. Zhang J, Rath AM, Boyer JC, Dumas JL, Menu Y, Chevrel JP. Radioanatomic study of the gastroduodenal venous trunk. *Surg Radiol Anat*. 1994;16:413-418.
29. Mori H, McGrath FP, Malone DE, Stevenson GW. The gastroduodenal trunk and its tributaries: CT evaluation. *Radiology*. 1992;182:871-877.
30. Ibukuro K, Ishii R, Fukuda H, Abe S, Tsukiyama T. Collateral venous pathways in the transverse mesocolon and greater omentum in patients with pancreatic disease. *AJR Am J Roentgenol*. 2004;182:1187-1193.
31. Nishihara T, Yamashita Y, Abe Y, Mitsuzaki K, Tsuchigame T, et al. Local extension of pancreatic carcinoma: assessment with thin-section helical CT versus with breath-hold fast MR imaging—ROC analysis. *Radiology*. 1999;212:445-452.
32. Sodickson A, Baeyens PF, Andriole KP, Prevedello LM, Nawfel RD, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. *Radiology*. 2009;251:175-184.
33. Bipat S, Phoa SS, van Delden OM, Bossuyt PM, Gouma DJ, et al. Ultrasonography, computed tomography, and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. *J Comput Assist Tomogr*. 2005;29:438-445.
34. Vachiranubhap B, Kim YH, Balci NC, Semelka RC. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging*. 2009;20:3-9.
35. Park HS, Lee JM, Choi HK, Hong SH, Han JK, Choi BI. Preoperative evaluation of pancreatic cancer: comparison of gadolinium-enhanced dynamic MRI with MR cholangiopancreatography versus MDCT. *J Magn Reson Imaging*. 2009;30:586-595.
36. Vellet AD, Romano W, Bach DB, Passi RB, Taves DH, Munk PL. Adenocarcinoma of the pancreatic ducts: comparative evaluation with CT and MR imaging at 1.5 T. *Radiology*. 1992;183:87-95.
37. Holalkere NS, Sahani DV, Blake MA, Halpern EF, Hahn PF, Mueller PR. Characterization of small liver lesions: added role of MR after MDCT. *J Comput Assist Tomogr*. 2006;30:591-596.
38. Sahani DV, Shah ZK, Catalano OA, Boland GW, Brugge WR. Radiology of pancreatic adenocarcinoma: current status of imaging. *J Gastroenterol Hepatol*. 2008;23:23-33.
39. Tsushima Y, Takano A, Taketomi-Takahashi A, Endo K. Body diffusion-weighted MR imaging using high b-value for malignant tumor screening: usefulness and necessity of referring to T2-weighted images and creating fusion images. *Acad Radiol*. 2007;14:643-650.
40. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer [see comment][summary for patients in *Ann Intern Med*. 2004;141:146]. *Ann Intern Med*. 2004;141:753-763.
41. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. *Gastrointest Endosc*. 1999;50:786-791.
42. Aliperti G. Complications related to diagnostic and therapeutic endoscopic retrograde cholangiopancreatography. *Gastrointest Endosc Clin N Am*. 1996;6:379-407.
43. Rose DM, Delbeke D, Beauchamp RD, Chapman WC, Sandler MP, et al. 18Fluorodeoxyglucose-positron emission tomography in the management of patients with suspected pancreatic cancer. *Ann Surg*. 1999;229:729-737; discussion 737-738.
44. Keogan MT, Tyler D, Clark L, Branch MS, McDermott VG, et al. Diagnosis of pancreatic carcinoma: role of FDG PET. *AJR Am J Roentgenol*. 1998;171:1565-1570.
45. Goh BK, Tan YM, Chung YF. Utility of fusion CT-PET in the diagnosis of small pancreatic carcinoma. *World J Gastroenterol*. 2005;11:3800-3802.
46. Alessio AM, Kinahan PE, Cheng PM, Vesselle H, Karp JS. PET/CT scanner instrumentation, challenges, and solutions. *Radiol Clin North Am*. 2004;42:1017-1032.
47. Yan L, McFaul C, Howes N, Leslie J, Lancaster G, et al. Molecular analysis to detect pancreatic ductal adenocarcinoma in high-risk groups. *Gastroenterology*. 2005;128:2124-2130.
48. Nakashima A, Murakami Y, Uemura K, Hayashidani Y, Sudo T, et al. Usefulness of human telomerase reverse transcriptase in pancreatic juice as a biomarker of pancreatic malignancy. *Pancreas*. 2009;38:527-533.
49. Comfort MW, Steinberg AG. Pedigree of a family with hereditary chronic relapsing pancreatitis. *Gastroenterology*. 1952;21:54-63.
50. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene [see comment]. *Nat Genet*. 1996;14:141-145.
51. Lowenfels AB, Maisonneuve P, DiMaggio EP, Elitsur Y, Gates LK Jr, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group [see comment]. *J Natl Cancer Inst*. 1997;89:442-446.
52. Lynch HT, Lanspa SJ, Fitzgibbons RJ Jr, Smyrk T, Fitzsimmons ML, McClellan J. Familial pancreatic cancer (Part 1): Genetic pathology review. *Nebr Med J*. 1989;74:109-112.
53. Hruban RH, Petersen GM, Ha PK, Kern SE. Genetics of pancreatic cancer. From genes to families. *Surg Oncol Clin N Am*. 1998;7:1-23.
54. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res*. 2004;64:2634-2638.
55. McFaul CD, Greenhalf W, Earl J, Howes N, Neoptolemos JP, et al. Anticipation in familial pancreatic cancer [see comment]. *Gut*. 2006;55:252-258.
56. Murphy KM, Brune KA, Griffin C, Sollenberger JE, Petersen GM, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. *Cancer Res*. 2002;62:3789-3793.
57. Neglia JP, FitzSimmons SC, Maisonneuve P, Schöni MH, Schöni-Affolter F, et al. The risk of cancer among patients with cystic fibrosis. Cystic Fibrosis and Cancer Study Group [see comment]. *N Engl J Med*. 1995;332:494-499.
58. Vitone LJ, Greenhalf W, McFaul CD, Ghaneh P, Neoptolemos JP. The inherited genetics of pancreatic cancer and prospects for secondary screening. *Best Pract Res Clin Gastroenterol*. 2006;20:253-283.
59. Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature*. 1998;391:184-187.
60. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology*. 2000;119:1447-1453.
61. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology*. 1999;116:1453-1456.
62. Lynch HT, Voorhees GJ, Lanspa SJ, McGreevy PS, Lynch JF. Pancreatic carcinoma and hereditary nonpolyposis colorectal cancer: a family study. *Br J Cancer*. 1985;52:271-273.
63. Lynch HT, Lynch JF. Hereditary nonpolyposis colorectal cancer. *Semin Surg Oncol*. 2000;18:305-313.

64. Landi S. Genetic predisposition and environmental risk factors to pancreatic cancer: a review of the literature. *Mutat Res*. 2009;681:299-307.
65. Geary J, Sasieni P, Houlston R, Izatt L, Eeles R, et al. Gene-related cancer spectrum in families with hereditary non-polyposis colorectal cancer (HNPCC). *Fam Cancer*. 2008;7:163-172.
66. Park JG, Park YJ, Wijnen JT, Vasen HF. Gene-environment interaction in hereditary nonpolyposis colorectal cancer with implications for diagnosis and genetic testing. *Int J Cancer*. 1999;82:516-519.
67. Rulyak SJ, Brentnall TA, Lynch HT, Austin MA. Characterization of the neoplastic phenotype in the familial atypical multiple-mole melanoma-pancreatic carcinoma syndrome. *Cancer*. 2003;98:798-804.
68. Goldstein AM, Fraser MC, Struwing JP, Hussussian CJ, Ranade K, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations [see comment]. *N Engl J Med*. 1995;333:970-974.
69. Whelan AJ, Bartsch D, Goodfellow PJ. Brief report: a familial syndrome of pancreatic cancer and melanoma with a mutation in the CDKN2 tumor-suppressor gene [see comment]. *N Engl J Med*. 1995;333:975-977.
70. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada [see comment]. *J Natl Cancer Inst*. 2006;98:1694-1706.
71. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. *J Med Genet*. 2005;42:711-719.
72. Fuchs CS, Colditz GA, Stampfer MJ, Giovannucci EL, Hunter DJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med*. 1996;156:2255-2260.
73. Silverman DT, Dunn JA, Hoover RN, Schiffman M, Lillemoe KD, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. *J Natl Cancer Inst*. 1994;86:1510-1516.
74. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, et al. A prospective cohort study of cigarette smoking and pancreatic cancer in Japan. *Cancer Causes Control*. 2002;13:249-254.
75. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA*. 1995;273:1605-1609.
76. Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. *Br J Cancer*. 2007;96:507-509.
77. Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005;92:2076-2083.
78. Michaud DS. Epidemiology of pancreatic cancer. *Minerva Chir*. 2004;59:99-111.
79. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology*. 2005;129:504-511.
80. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology*. 2001;120:682-707.
81. Talamini G, Falconi M, Bassi C, Sartori N, Salvia R, et al. Incidence of cancer in the course of chronic pancreatitis. *Am J Gastroenterol*. 1999;94:1253-1260.
82. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer [see comment]. *Gastroenterology*. 1995;109:247-251.
83. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group [see comment]. *N Engl J Med*. 1993;328:1433-1437.
84. Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. *Pancreas*. 1994;9:62-66.
85. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348:1625-1638.
86. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer [see comment]. *JAMA*. 2001;286:921-929.
87. Ji BT, Hatch MC, Chow WH, McLaughlin JK, Dai Q, et al. Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Int J Cancer*. 1996;66:432-437.
88. Kloppel G, Solcia E, Longnecker DS, Capella C, Sobin LH. *World Health Organization International Histological Classification of Tumours. Histological Typing of Tumours of the Exocrine Pancreas*. Berlin, Germany; Springer: 1996.
89. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatol*. 2006;6:17-32.
90. Moparty B, Brugge WR. Approach to pancreatic cystic lesions. *Curr Gastroenterol Rep*. 2007;9:130-135.
91. Sahani DV, Lin DJ, Venkatesan AM, Sainani N, Mino-Kenudson M, et al. Multidisciplinary approach to diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas. *Clin Gastroenterol Hepatol*. 2009;7:259-269.
92. Sahani DV, Miller JC, del Castillo CF, Brugge WR, Thrall JH, Lee SI. Cystic pancreatic lesions: classification and management. *J Am Coll Radiol*. 2009;6:317-320.
93. Rulyak SJ, Kimmey MB, Veenstra DL, Brentnall TA. Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds. *Gastrointest Endosc*. 2003;57:23-29.
94. Rubenstein JH, Scheiman JM, Anderson MA. A clinical and economic evaluation of endoscopic ultrasound for patients at risk for familial pancreatic adenocarcinoma. *Pancreatol*. 2007;7:514-525.
95. Gemmel C, Eickhoff A, Helmstädter L, Riemann JF. Pancreatic cancer screening: state of the art. *Expert Rev Gastroenterol Hepatol*. 2009;3:89-96.
96. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer [erratum appears in *Ann Intern Med*. 2000;132:419]. *Ann Intern Med*. 1999;131:247-255.
97. Kimmey MB, Bronner MP, Byrd DR, Brentnall TA. Screening and surveillance for hereditary pancreatic cancer. *Gastrointest Endosc*. 2002;56(4 suppl):S82-86.
98. Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study [see comment]. *Clin Gastroenterol Hepatol*. 2006;4:766-781; quiz 665.
99. Poley JW, Kluij I, Gouma DJ, Harinck F, Wagner A, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol*. 2009;104:2175-2181.
100. Canto MI. Screening for pancreatic neoplasia in high-risk individuals: who, what, when, how? *Clin Gastroenterol Hepatol*. 2005;3(7 suppl 1):S46-48.
101. Antwi K, Hostetter G, Demeure MJ, Katchman BA, Decker GA, et al. Analysis of the plasma peptidome from pancreas cancer patients connects a peptide in plasma to overexpression of the parent protein in tumors. *J Proteome Res*. 2009;8:4722-4731.
102. Thompson D, Easton DF; Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers [see comment]. *J Natl Cancer Inst*. 2002;94:1358-1365.